Quantifying the Area at Risk in Reperfused ST-Segment–Elevation Myocardial Infarction Patients Using Hybrid Cardiac Positron Emission Tomography–Magnetic Resonance Imaging

Heerajnarain Bulluck, MBBS*; Steven K. White, BSc, MBChB*; Georg M. Fröhlich, MD; Steven G. Casson, MA, MB BChir, MSc; Celia O’Meara, BSc; Ayla Newton, BSc; Jennifer Nicholas, PhD; Peter Weale, BA, DCR(R); Simon M.Y. Wan, MD; Alex Sirker, PhD; James C. Moon, MD; Derek M. Yellon, DSc, PhD; Ashley Groves, MD, PhD; Leon Menezes, BM BCh; Derek J. Hausenloy, MD, PhD

**Background**—Hybrid positron emission tomography and magnetic resonance allows the advantages of magnetic resonance in tissue characterizing the myocardium to be combined with the unique metabolic insights of positron emission tomography. We hypothesized that the area of reduced myocardial glucose uptake would closely match the area at risk delineated by T2 mapping in ST-segment–elevation myocardial infarction patients.

**Methods and Results**—Hybrid positron emission tomography and magnetic resonance using 18F-fluorodeoxyglucose (FDG) for glucose uptake was performed in 21 ST-segment–elevation myocardial infarction patients at a median of 5 days. Follow-up scans were performed in a subset of patients 12 months later. The area of reduced FDG uptake was significantly larger than the infarct size quantified by late gadolinium enhancement (37.2±11.6% versus 22.3±11.7%; \(P<0.001\)) and closely matched the area at risk by T2 mapping (37.2±11.6% versus 36.3±12.2%; \(P=0.10\), \(R=0.98\), bias 0.9±4.4%). On the follow-up scans, the area of reduced FDG uptake was significantly smaller in size when compared with the acute scans (19.5 [6.3%–31.8%] versus 44.0 [21.3%–55.3%]; \(P=0.002\)) and closely correlated with the areas of late gadolinium enhancement (\(R=0.98\)) with a small bias of 2.0±5.6%. An FDG uptake of ≥45% on the acute scans could predict viable myocardium on the follow-up scan. Both transmural extent of late gadolinium enhancement and FDG uptake on the acute scan performed equally well to predict segmental wall motion recovery.

**Conclusions**—Hybrid positron emission tomography and magnetic resonance in the reperfused ST-segment–elevation myocardial infarction patients showed reduced myocardial glucose uptake within the area at risk and closely matched the area at risk delineated by T2 mapping. FDG uptake, as well as transmural extent of late gadolinium enhancement, acutely can identify viable myocardial segments. (*Circ Cardiovasc Imaging, 2016;9:e003900. DOI: 10.1161/CIRCIMAGING.115.003900.*)

**Key Words:** area at risk, cardiovascular magnetic resonance imaging, F-flurodeoxyglucose, hybrid PET-MR imaging, infarct size, positron emission tomography, ST-segment–elevation myocardial infarction, T2 mapping, viability
MR to be combined with the metabolic insights provided by PET, without requiring an acutely unwell patient to undergo 2 separate scans and obviating complex and potentially imprecise coregistration of separately acquired PET and MR data sets. To date, there has been limited experience with hybrid PET-MR imaging of the heart.\textsuperscript{5–7} T2-weighted MR imaging of myocardial edema has been used to quantify the AAR in STEMI patients, a prerequisite for calculating myocardial salvage—a critical measure of efficacy in cardioprotection studies.\textsuperscript{6} Hyperacute PET-MR imaging of the reperfused heart, therefore, provides the opportunity to investigate cardiac metabolism in salvaged, reversibly injured myocardium within the AAR. The area of reduced myocardial glucose uptake has recently been shown to overestimate the AAR assessed by endocardial surface area (ESA).\textsuperscript{11} We hypothesized that the area of reduced myocardial glucose uptake would closely match the AAR delineated by T2 mapping in STEMI patients treated by primary percutaneous coronary intervention (PPCI).

**Methods**

**Study Population**

We performed a single-center study of 22 STEMI patients treated by PPCI recruited over a 7-month period. Study exclusion criteria were as follows: ≤ 545 years of age (to attenuate any theoretical higher risk from ionizing radiation in younger patients); diabetes mellitus (because preexisting metabolic/glycemic derangement may affect clarity of initial results); previous MI; and standard recognized contraindications to MR. All eligible patients provided informed and written consent. The study was approved by the UK National Research Ethics Service.

**Hybrid PET-MR Cardiac Imaging Protocol**

Patients underwent hybrid PET-MR imaging at a median of 5 (4–6) days after PPCI using an integrated whole-body PET-MR (3.0 Tesla) scanner (Biograph mMR, Siemens Healthcare, Erlangen, Germany; Figure 1). A subset of patients underwent a follow-up scan at 12 months.\textsuperscript{17} 18F-fluorodeoxyglucose (FDG) was used to assess resting myocardial glucose metabolism. Subjects fasted for a minimum of 6 hours followed by 75 g of oral glucose 2 hours before the scan, and 45 to 60 minutes later, insulin was administered as previously described,\textsuperscript{18} followed by intravenous FDG (mean activity of 248±15 MBq) at a mean of 73±12 minutes before PET image acquisition.

A standard cardiac MR imaging protocol,\textsuperscript{15}\textsuperscript{21} including cine imaging, and T2 mapping and late gadolinium enhancement (LGE) imaging was performed simultaneously with the FDG-PET acquisition after single breath-hold attenuation correction. LGE imaging was performed using a standard segmented fast low-angle shot 2-dimensional inversion-recovery gradient echo sequence 10 to 15 minutes after the injection of Gadoterate meglumine (Gd-DOTA marketed as Dotarem, Guerbert S.A., Paris, France) at a dose of 0.1 mmol/kg, and T2 maps (Works in Progress, software WIP No 699, Siemens Healthcare, Frimley, UK) were acquired as previously described.\textsuperscript{19} In brief, 3 single-shot images at different T2 preparation times (0, 24, and 55 ms, respectively) using the following parameters were acquired: repetition time=3×R-R interval; acquisition matrix=116×192; flip angle=65°; slice thickness=6 mm with 4 mm gap; field of view adjusted according to subject size (320–400 mm). Motion correction and fitting were performed to estimate coefficients of the decay function, which was subsequently used to estimate T2 relaxation times. An in-built specific color look-up table was used to output the final color T2 maps, consisting of pixel-wise T2 values. A full stack of short-axis slices was acquired to cover the left ventricular (LV) from base to apex—each MR modality matching exactly the same slice position.

FDG-PET images were acquired with one-bed position, gated by electrocardiography, and comprised of 3-dimensional isotropic image reconstruction (voxel size, 2×2×2 mm\textsuperscript{3}) using Poisson ordered subset expectation maximization with 21 subsets and 3 iterations, a Gaussian filter with 5.0-mm full-width at half maximum, and a 344×344 image matrix to obtain summed average FDG-PET images. A 4-compartment model PET attenuation map was calculated using the MR capabilities of the machine using fat-only and water-only Dixon-based sequences for automatic PET attenuation correction.\textsuperscript{15}

**Image Analysis**

**Co-Localization of the MI Territory With FDG Uptake**

Co-localization of the MI territory with FDG uptake was evaluated using fused FDG-LGE images created by fusing individual end-diastolic LGE short-axis slices with the summed static FDG-PET images using OsiriX freeware (Version 5.8.5, Geneva, Switzerland). The fused images were then visually assessed to identify areas of LGE and reduced FDG uptake.

**Quantification of AAR, MI Size, and FDG Uptake**

Quantification of LV volumes, LV mass, LV ejection fraction, AAR by T2 mapping, regions of reduced FDG uptake, and MI size were performed using CVI\textsuperscript{42} software (Version 5.1.0, Calgary, Canada). As described earlier, each end-diastolic LGE slice was initially fused with the summed static FDG-PET images, extracting both a fused and a slice-matched nonfused FDG image. These nonfused FDG LV short-axis slices, along with their corresponding T2 maps, were used for quantification. The epicardial and endocardial borders were first manually traced on the T2 maps and LGE images and copied onto the FDG images with minimal manual adjustment. The MI size was quantified by the Otsu-auto-thresholding technique. Two blinded operators independently analyzed the T2 maps (Otsu-auto-thresholding) and FDG-PET images (manual delineation of the regions with reduced FDG uptake on the summed images with visual optimization of the window settings by 2 operators). Areas of MVO were included as part of the MI and AAR on the LGE images and T2 maps and any obvious blood pool or pericardial partial voluming and artifacts were manually corrected. One operator subsequently used Otsu-auto-thresholding,
full width half maximum, and reduction in signal intensity 2, 3, 4, and 5 standard deviations (SD) from the remote myocardium to quantify the regions of reduced FDG uptake. All of the LV short axis slices from base to apex were analyzed, and the final extent of abnormal myocardium was expressed as a percentage of the LV volume. Polar maps for the FDG images were generated (Xeleris Version 3.0; GE Healthcare, Milwaukee, WI) and displayed relative segmental FDG uptake as per the American Heart Association model, normalized to the highest signal intensity for that patient set at 100%. A second method to quantify the reduction in FDG uptake in the infarct-related territory was also performed by using a threshold of <50% on the acute scan polar maps. A threshold of ≥50% on the follow-up polar maps was used for identifying viable segments.16

Segmental analysis was performed using CVI42 software for early gadolinium enhancement, LGE, and T2 maps and displayed according to the modified 16-segment (excluding the apex) American Heart Association model.17 The early gadolinium enhancement images were visually analyzed by 2 experienced investigators, and segments with a hypo-intense core were visually scored 0 or 1 for absence or presence of early MVO. Mean transmural extent of LGE was quantified for each short axis slice, and mean segmental T2 values were also automatically generated, displayed according to the modified 16-segment American Heart Association model. Segmental wall motion analysis was visually performed by 2 experienced investigators and scored as 0 for normal; 1 for mild/moderate hypokinesis; 2 for severe hypokinesis; 3 for akinesis; and 4 for dyskinesis.18 A reduction in segmental wall motion score of ≥1 at follow-up was defined as an improvement in segmental wall motion.

Coronary Angiographic Analysis

Coronary angiograms were analyzed by 2 independent experienced investigators using the Bypass Angioplasty Revascularisation Investigation (BARI) and the modified Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) coronary angiography jeopardy scores19 to provide an MR-independent estimate of the AAR.

Statistical Analysis

Continuous data were expressed as mean±SD or median (interquartile range) for variables showing departure from a normal distribution. Categorical data were reported as frequencies and percentages. Intraclass correlation coefficients for interobserver agreement20 were calculated for the T2 mapping and FDG-PET quantification by using single measures in a 2-way random model for absolute agreement. Paired tests were used to compare measurements made within the same patient using 2 techniques at 1 time point (eg, AAR by T2 mapping and FDG-PET) or using the same technique at 2 time points (eg, reduction in FDG uptake between the acute and follow-up scans). Pearson’s correlation coefficient was used to assess intermethod correlation. Bland–Altman analysis was performed to assess agreement and bias detection between methods and presented as bias±2 SD. Variances between methods were compared using Pitman’s test. Receiver operating characteristic (ROC) analyses were performed to assess the diagnostic performance for LGE, FDG, and T2 on the acute scan for detecting viable myocardium and predicting segmental wall motion recovery. All statistical tests were 2-tailed, and P<0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 22 (IBM Corporation, IL). MedCalc version 15.6.1 (Medcalc Software Ostend, Belgium) was also used for ROC curve comparison using the method described by Delong et al21 and for correlation coefficient comparison described by Hinkle et al.22

Results

Twenty-one patients completed the full imaging protocol at a median of 5 (4–6) days (1 patient was unexpectedly claustrophobic)—76% were male, and the median time between chest pain onset and PPCI was 247 (119–687) minutes. None of the patients had left bundle branch block. More detailed patient characteristics and coronary angiographic details are presented in Table 1. Twelve patients had a follow-up scan at a median of 12 (11–14) months after PPCI.

Area of Reduced FDG Uptake Is Larger Than MI Size by LGE-MR

From the fused FDG-LGE images, 20 out of 21 patients had reduced FDG uptake in the same territory of the MI location. The area of reduced FDG uptake was significantly larger than the area of LGE (37.2±11.6% with FDG-PET versus 22.3±11.7% with LGE-MR; P<0.001; Table 2). Figures 2 and 3 show representative images of patients with a transmural MI (minimal myocardial salvage) and a subendocardial MI (significant myocardial salvage), respectively.

Area of Reduced FDG Uptake Delineates the AAR by T2 Mapping

There was excellent per-patient interobserver agreement for the AAR by T2 mapping and manual delineation of reduced FDG uptake, with an intraclass correlation coefficient of 0.93 (95% confidence interval [CI] 0.83–0.97; P<0.001) and 0.94 (95% CI 0.85–0.98; P<0.001), respectively. Figure 4 and Table 3 show the performance of the different thresholding techniques when compared with manual delineation of the area of reduced FDG uptake. The 2 SD thresholding technique performed best with excellent correlation and agreement (P=0.07, intraclass correlation 0.99, R=0.99, bias of −0.9±4.33%) and was used for subsequent analyses.

The area of reduced FDG uptake closely matched the AAR delineated by T2 mapping (37.2±11.6% with FDG-PET versus 36.3±12.2% with T2 mapping; P=0.10). There was an excellent correlation and agreement between the area of reduced FDG uptake and the AAR by T2 mapping (R=0.98, bias 0.9±4.4%, no difference between their variances; P=0.28; Figure 5A and 5B). When using the 50% threshold on the polar maps to quantify the area of reduced FDG uptake, there was no difference when compared with the AAR by T2-mapping (37.8±16.9% with FDG-PET versus 36.3±12.2% with T2 mapping; P=0.10). The correlation between them was 0.90 but there was a wider limit of agreement on Bland Altman analysis (bias of 2.0±15.6%). Furthermore, Pitman’s test confirmed a difference in the AAR by the 2 methods (P<0.05). For patients with an AAR of <35%, T2-mapping had a trend to give a higher AAR than FDG uptake, whereas for an AAR of >35%, T2 mapping tended to be lower than FDG uptake (Figure 5C and 5D).

Area of Reduced FDG Uptake Compared With BARI and Modified APPROACH Scores

The area of reduced FDG uptake correlated well with the MR-independent estimates of the AAR using the BARI and modified APPROACH coronary angiography scores but overestimated the AAR (37.2±11.6% with FDG-PET versus 28.7±8.3% with BARI score, R=0.79, P<0.001 and bias of 8.4±14.2%; and 37.2±11.6% with FDG-PET versus 29.4±9.8% with APPROACH score, R=0.71, P<0.001 and bias of 8.7±17.2%, respectively).
Hybrid Cardiac PET-MR Follow-Up Scans

The areas of reduced FDG uptake on the follow-up scans were significantly lower than those observed on the acute scans (Median [IQR]: 19.5 [6.3%–31.8%] follow-up scan versus 44.0 [21.3%–55.3%] acute scan, P=0.002) and correlated closely (R 0.98) with the areas of LGE on the follow-up scans. The areas of reduced FDG uptake were more similar to the area of LGE on the follow-up scan (19.5 [6.3%–31.8%] FDG-PET versus 19.0 [2.0%–28.0%] LGE-MR, P=0.04, bias of 2.0±5.6%; Figure 6 and Table 4).

Figure 7 illustrates the differences in FDG uptake between the acute and follow-up scans of 2 patients with different myocardial salvage.

Reduced FDG Uptake in the Remote Myocardium

In one patient presenting with an acute inferior STEMI, there was an additional area of reduced FDG uptake in the remote

Table 1. Patients Clinical Characteristics and Coronary Angiographic Details

<table>
<thead>
<tr>
<th>Details</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>21</td>
</tr>
<tr>
<td>Male</td>
<td>16 (76%)</td>
</tr>
<tr>
<td>Age</td>
<td>59±10</td>
</tr>
<tr>
<td>Previous coronary artery disease*</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.4±3.4</td>
</tr>
<tr>
<td>Chest pain index to PPCI time, min</td>
<td>247 [119–687]</td>
</tr>
</tbody>
</table>

Infarct artery, %

- LAD: 13 (62)
- Proximal: 6 (46)
- Mid: 6 (46)
- Distal: 1 (8)
- RCA: 8 (38)
- Proximal: 3 (37)
- Mid: 2 (25)
- Distal: 3 (37)

Pre-PPCI TIMI flow, %

- 0: 16 (76)
- 1: 4 (19)
- 2: 1 (5)
- 3: 0 (0)

Post-PPCI TIMI flow, %

- 0: 1 (5)
- 1: 0 (0)
- 2: 2 (9)
- 3: 18 (86)

Number of vessels

- Single vessel disease: 16 (76)
- Double vessel disease: 5 (24)

AAR

- BARI score, % LV volume: 28.7±8.3
- APPROACH score, % LV volume: 29.4±9.8

Treatment: during PPCI

- Aspirin: 21 (100%)
- Clopidogrel: 1 (5%)
- Ticagrelor: 18 (86%)
- Prasugrel: 2 (9%)
- Heparin: 14 (67%)

(Continued)

Table 2. Hybrid PET-MR Findings on Acute Scan

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from PPCI to hybrid PET-MR scan, days</td>
<td>5 [4–6]</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>50±11 (Normal range 58–76)</td>
</tr>
<tr>
<td>End diastolic volume, mL</td>
<td>138±22 (Normal range 113–196)</td>
</tr>
<tr>
<td>Left ventricular mass, g</td>
<td>150±46 (Normal range 107–184)</td>
</tr>
<tr>
<td>Presence of MVO, %</td>
<td>11 (46)</td>
</tr>
<tr>
<td>Presence of apical thrombus, %</td>
<td>4 (19)</td>
</tr>
<tr>
<td>MI size by LGE MR, % LV volume</td>
<td>22.3±11.7</td>
</tr>
<tr>
<td>AAR by T2-mapping MR, % LV volume</td>
<td>36.3±12.2</td>
</tr>
<tr>
<td>AAR by FDG-PET, % LV volume</td>
<td>37.2±11.6</td>
</tr>
</tbody>
</table>

Data are mean±SD. AAR indicates area at risk; FDG, 18F-fluorodeoxyglucose; LGE, late gadolinium enhancement; LV, left ventricle; MI, myocardial infarction; MR, magnetic resonance; MVO, microvascular obstruction; PET, positron emission tomography; and PPCI, primary percutaneous coronary intervention.
myocardium within the nonobstructed left anterior descending coronary artery, with the follow-up scan showing improved FDG uptake within this remote area (Figure 8). This patient was excluded from any comparison given that there was reduced FDG uptake outside of the infarct-related territory.

**Acute Scans to Assess Viability**

Using an FDG uptake of ≥50% to indicate viable myocardium on the follow-up scan, the transmural extent of LGE on both the acute scan (area under the curve [AUC] on the ROC curve 0.93, 95% CI 0.89–0.97) and the follow-up scan (AUC on the ROC curve 0.95, 95% CI 0.92–0.99) performed equally well at predicting viable myocardium (P=0.13). Both acute LGE and follow-up LGE performed better than acute FDG uptake (AUC on the ROC curve 0.92, 95% CI 0.85–0.98) at detecting viable myocardium (P<0.001 and P=0.01, respectively, for ROC curve comparison). The cut-off value of <50% transmural LGE on the acute scan had a sensitivity of 88% and specificity of 90% and on the follow-up scan had a sensitivity of 94% and specificity of 90%. The optimal cut-off for FDG uptake on the acute scan was a value of ≥45%, giving a sensitivity of 85% and specificity of 95% to identify viable myocardium on follow-up. T2 performed the least well compared with LGE and FDG with an AUC of 0.79, 95% CI 0.71 to 0.87, and a cut-off value of 55 ms had a sensitivity and specificity of 76%.

**Segmental Wall Motion Recovery**

Segmental wall motion was assessed in the 12 patients with acute and follow-up scans. Four segments were excluded (because of incidental chronic infarct). Out of the remaining 188 segments, 94 segments (50%) had no wall motion abnormalities. The remaining 94 segments had wall motion scores as follows: (1) 20 segments; (2) 23 segments; and (3) 51 segments. There was a similar correlation between wall motion score and FDG uptake on both the acute and follow-up scans (R=−0.59 versus R=−0.65, P=0.51).

Out of 94 segments with abnormal wall motion, 19 segments (20%) had no LGE and had lower T2 values and higher FDG uptake than the 75 segments (80%) with the presence of LGE (T2: 48.9±5.1 ms versus 57.2±8.1 ms, P<0.001; FDG uptake: 63±12 versus 42±17, P<0.001). All segments with no LGE showed complete recovery of wall motion at 1 year.
There was no correlation between the wall motion score and FDG uptake in these later segments ($R = -0.06$, $P = 0.82$).

Among the segments with LGE, 34 segments (45%) had $< 50\%$ transmural LGE and 41 segments (55%) had $\geq 50\%$ transmural LGE with no difference in T2 values between these 2 groups (T2: 55.7±8.1 ms versus 58.4±7.9 ms, $P = 0.18$). However, FDG uptake was significantly lower in segments with $\geq 50\%$ transmural LGE (FDG uptake for LGE $< 50\%$ 50±15 versus 35±16 for LGE $\geq 50\%$; $P < 0.001$), and these segments were also least likely to recover regional wall motion (LGE $< 50\%$: 27/34 [79\%] recovered wall motion compared with LGE $\geq 50\%$: 20/41 [49\%] recovered wall motion, $P = 0.006$).

All segments with early MVO had $\geq 50\%$ transmural LGE. When considering only segments with $\geq 50\%$ transmural LGE, those with early MVO ($n = 20$, 49\%) had lower T2 values (consistent with intramyocardial hemorrhage) but similar level of FDG uptake compared with those without early MVO, and these segments were also least likely to recover wall motion (T2: 55.4±5.9 ms versus 62.0±8.6 ms, $P = 0.01$; FDG uptake: 31±14 versus 39±17, $P = 0.09$; wall motion recovery: 5/20 [25\%] for those with early MVO versus 15/21 for those without—75\%, $P = 0.004$).

ROC curve analysis showed acute LGE and FDG performed equally well (AUC 0.82, 95% CI 0.72–0.90 and 0.82, 95% CI 0.72–0.90; $P = 0.94$) but better than T2 (AUC 0.66, 95% CI 0.55–0.76; $P = 0.02$ and $P = 0.04$ respectively) to predict segmental wall motion recovery.

**Discussion**

Using hybrid cardiac PET-MR imaging in reperfused STEMI patients, we found that the area of reduced myocardial glucose...
uptake by FDG-PET imaging closely matched the AAR delineated by T2 mapping. In STEMI patients with minimal myocardial salvage, the areas of reduced FDG uptake were confined to the areas of LGE, confirming that cardiac metabolism was impaired within the irreversibly injured myocardium within the MI. However, in patients with significant myocardial salvage, the areas of reduced FDG uptake extended beyond the areas of LGE and closely matched the AAR delineated by T2 mapping. This demonstrates that in patients with significant myocardial salvage, impaired cardiac metabolism was not confined to areas of irreversibly injured myocardium within the MI, but also included the reversibly injured salvaged myocardium within the AAR. In a subset of patients who had 12-month follow-up scans, the areas of reduced FDG uptake were significantly lower than those observed on the acute scans and were now confined to the areas of LGE only. This demonstrates normalization of cardiac metabolism within reversibly injured salvaged myocardium in the AAR, leaving areas of reduced FDG uptake in irreversible (nonviable) tissue.

The reliable and accurate measurement of the AAR is required to assess myocardial salvage in clinical studies investigating novel cardioprotective interventions in reperfused STEMI patients. Cardiac MR allows the retrospective delineation of the AAR in STEMI patients treated by PPCI and depends on the ability of T2-weighted imaging to delineate the extent of myocardial edema within the AAR. It has been validated by histology in animal MI models and by angiography jeopardy scores and myocardial SPECT imaging in STEMI patients. An alternative method to estimate the AAR is to measure the ESA of LGE. However, unlike T2-weighted short tau inversion recovery imaging and T2-mapping, ESA is unable to quantify the AAR in patients with minimal or absent infarction. Furthermore, ESA has been shown to underestimate the AAR in STEMI patients when compared with T2-weighted imaging. This finding was confirmed in a recent study, in which the area of reduced FDG uptake was shown to overestimate the AAR delineated by the ESA in reperfused STEMI patients.

There is currently no gold standard method for accurately quantifying the reduction in FDG uptake, and so we used manual delineation by 2 blinded operators as our reference standard and compared it to 6 other established thresholding techniques. In this study, we found that a 2SD thresholding technique performed best for quantifying the areas of reduced myocardial glucose uptake. When using a threshold of 50% of peak—more conventional in the field of PET imaging—we found the limits of agreement between FDG-PET and T2 mapping were wide, likely because of the inherent differences in the 2 techniques used, such as differences in spatial resolution and acquisition phase during the cardiac cycle.

The mechanism for the reduced FDG uptake observed in reversibly injured salvaged myocardium is not clear. Animal models have been used to elucidate the metabolic changes occurring in reversibly injured and stunned myocardium but because of the different ischemia/reperfusion protocols used and different baseline metabolic state of the animals before FDG administration, results from these studies regarding glucose and free fatty acid metabolism varied. However, putting these studies into context, it may be plausible that the reversibly injured but stunned myocardium preferentially uptakes more glucose than free fatty acid after a period of fasting compared with the normal myocardium but has delayed glucose metabolism. Therefore, after an oral glucose load, the reversibly injured myocardium has a reduced FDG uptake but subsequently normalizes on the follow-up scan.

Although a threshold of ≥50% of FDG uptake has been used to identify viable myocardium in the setting of stable coronary artery disease, the utility of FDG uptake in the acute setting has not been extensively studied. We have provided further insights into the definition and performance of LGE and FDG to detect viability in the acute setting, using the FDG uptake on the corresponding follow-up scan as gold standard. Shirasaki et al has previously suggested a cut-off of 40% to detect viable myocardium, but FDG PET imaging was performed 2 weeks post acute MI, and they used segmental wall motion recovery as the definition for viability. Rischpler et al used a cut-off of ≥50% in the acute setting but no follow-up FDG PET was performed for comparison. Therefore, our study is the first to provide validation of FDG uptake in the acute MI setting by using follow-up FDG as the gold standard for viability.

We have also provided important insights into segmental wall motion recovery after acute MI. Dysfunctional segments

| Table 4. Hybrid PET-MR Findings in 12 Patients With Acute and Follow-Up Scans |
|---------------------------------|---------|---------|-----------|
|                                  | Acute Scan | Follow-Up Scan | P Value |
| LVEF, %                          | 52 (47–59) | 57 (47–68) | 0.03* |
| End diastolic volume, mL         | 147 (126–159) | 152 (133–168) | 0.33 |
| Left ventricular mass, g         | 150 (122–167) | 110 (90–122) | 0.002* |
| LV size, % LV volume             | 27.8 (8.1–35.5) | 19.0 (2.0–28.0) | 0.005* |
| FDG-PET, % LV volume             | 44.0 (21.3–55.3) | 19.5 (6.3–31.8) | 0.002* |

Data are median (Interquartile range). FDG-PET indicates 18F-fluorodeoxyglucose positron emission tomography; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and MR, magnetic resonance.

*Statistical significance.
without LGE showed increased edema and reduced glucose metabolism yet recovered completely. Dysfunctional segments with early MVO showed evidence of intramyocardial hemorrhage and reduced glucose metabolism and were least likely to recover wall motion. Segments with predominantly reversibly injured myocardium were equally edematous compared with segments with predominantly irreversibly injured myocardium but differed in glucose metabolism. T2 did not perform as well as LGE and FDG on the acute scan to predict functional recovery because of the paramagnetic properties of intramyocardial hemorrhage reducing the T2 signal. 

Despite only having a small number of segments without LGE but with wall motion abnormality, the lack of correlation between FDG uptake and wall motion score may be explained by the reduction in wall thickening, giving rise to reduced FDG uptake appearance on the summed static FDG images.

Limitations of Study
There were several exclusions in our study (diabetics, age <45 years, previous MI, known contraindications for MR), and our findings are limited to a selected group of STEMI patients. Being a low-volume PPCI center and compounded by the strict inclusion criteria, we only managed to recruit a small number of patients. Follow-ups were performed in 12 patients only but these were sufficient to confirm recovery of FDG uptake in salvage myocardium. Current techniques for PET attenuation correction are known to increase image noise, cause image distortion, and artifacts, and therefore, manual adjustment of copied endocardial and epicardial contours, assisted by visual optimization of window settings, was required. The significant difference between the paired scans (acute and follow-up) in 12 patients supports the study findings of a reduction in FDG uptake in the AAR within a week of an acute STEMI. However, it is possible that by the use of summed static FDG-PET data, insufficient count recovery in stunned hypokinetic areas around the infarct border zone may have introduced an over-estimation in the correlation between the FDG uptake and T2 mapping. The development of techniques for PET-MR cardiac phase registration, and partial volume correction, may improve future image analysis to confirm these findings.

Summary and Conclusions
We have demonstrated that the area of reduced myocardial glucose uptake within the AAR closely matched the AAR

Figure 7. 18F-fluorodeoxyglucose (FDG) uptake in acute and follow-up hybrid cardiac positron emission tomography–magnetic resonance (PET-MR) scans. Representative LV short-axis slices of FDG-PET and late gadolinium enhancement (LGE)-MR images in 2 ST-segment–elevation myocardial infarction (STEMI) patients with differing degrees of myocardial salvage. Patient A presented with an anterior STEMI and transmural myocardial infarction (red arrow) on the acute scan. On the follow-up scan, there is no significant change in the area of reduced FDG uptake, confirming nonviable myocardium in the infarct zone. Patient B presented with an inferior subendocardial myocardial infarction (red arrow). The area of reduced FDG uptake is substantially larger than the area of LGE, indicating significant myocardial salvage. On the follow-up scan, there is a significant reduction in the area of reduced FDG uptake which is now restricted to the infarct zone.

Figure 8. Reduced myocardial glucose uptake in remote myocardium. One study patient with a midnight coronary artery ST-segment–elevation myocardial infarction (STEMI) had an area of reduced 18F-fluorodeoxyglucose (FDG) uptake (white arrow) matching the inferior infarct by late gadolinium enhancement (LGE; red arrow) and the area at risk (AAR) in the inferior left ventricular (LV) wall by T2 mapping (black arrow). There was an additional area of reduced FDG uptake in the anterior and antero-septal walls (yellow arrows) in remote myocardium. The follow-up scan showed improvement in FDG uptake in the anterior and antero-septal walls of the remote myocardium.
delineated by T2 mapping. Furthermore, FDG uptake, transmural extent of LGE, and T2 values on the acute scan seem to predict subsequent myocardial viability and segmental wall motion recovery. With the advent of novel biological tracers, hybrid cardiac PET-MR has the potential to provide further insights into the pathophysiology of acute MI and subsequent post-MI LV remodeling.

Acknowledgments

We express our gratitude to the staff and patients at the UCLH Heart Hospital. The investigational sequence for T2-mapping imaging was provided under a research collaboration agreement with Siemens Healthcare.

Sources of Funding

This research study was funded by the British Heart Foundation (grant number FS/10/039/28270) and the Rosetrees Trust and was supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. S.K. White is supported by British Heart Foundation Clinical Research Training Fellowship (grant number FS/10/72/28568).

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Hybrid positron emission tomography–magnetic resonance (PET-MR) imaging combines the power of magnetic resonance tissue characterization with the ability to investigate and colocalize cellular processes by PET. We used 18F-fluorodeoxyglucose (FDG)–PET to study myocardial metabolism in the setting of a reperfused myocardial infarction (MI) and showed that reduced myocardial glucose uptake occurs in reversibly (as well as irreversibly) injured myocardium, and these areas matched the area at risk delineated by T2-mapping magnetic resonance. This new observation offers an alternative measure of the area at risk in trials assessing the benefit of cardioprotective therapies and has important clinical implications for the accurate assessment of viability by FDG–PET to guide revascularization in the acute phase after an acute MI. The finding that late gadolinium enhancement and FDG perform equally well in predicting functional recovery supports the use of either modality in centers where only one might be available. Although hybrid PET–MR is not yet widely available, it has cost implications and involves some radiation exposure. This study highlights its utility for validation in cardiovascular research and in providing novel mechanistic and pathophysiological insights in acute MI.
Quantifying the Area at Risk in Reperfused ST-Segment–Elevation Myocardial Infarction Patients Using Hybrid Cardiac Positron Emission Tomography – Magnetic Resonance Imaging

Heerajnarain Bulluck, Steven K. White, Georg M. Fröhlich, Steven G. Casson, Celia O'Meara, Ayla Newton, Jennifer Nicholas, Peter Weale, Simon M.Y. Wan, Alex Sirker, James C. Moon, Derek M. Yellon, Ashley Groves, Leon Menezes and Derek J. Hausenloy

_Circ Cardiovasc Imaging_. 2016;9:e003900
doi: 10.1161/CIRCIMAGING.115.003900

_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/9/3/e003900

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Imaging_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Imaging_ is online at:
http://circimaging.ahajournals.org/subscriptions/